Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition

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Abstract

Studies assessing the effects of vitamin D or calcium intake on breast cancer risk have been inconclusive. Furthermore, few studies have evaluated them jointly. This study is the largest so far examining the association of dietary vitamin D and calcium intake with breast cancer risk in the European Prospective Investigation into Cancer and Nutrition.

During a mean follow-up of 8.8 years, 7,760 incident invasive breast cancer cases were identified among 319,985 women. Multivariable Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for pre- and postmenopausal breast cancer risk.

Comparing the highest with the lowest quintile of vitamin D intake, HR and 95% CIs were 1.07 (0.87-1.32) and 1.02 (0.90-1.16) for pre- and postmenopausal women, respectively. The corresponding HR and 95% CIs for calcium intake were 0.98 (0.80-1.19) and 0.90 (0.79-1.02), respectively. For calcium intake in postmenopausal women, the test for trend was borderline statistically significant (p_{trend}=0.05). There was no significant interaction between vitamin D and calcium intake and cancer risk ($p_{interaction}$=0.57 and 0.22 in pre- and postmenopausal women, respectively).

In this large prospective cohort, we found no evidence for an association between dietary vitamin D or calcium intake and breast cancer risk.

Keywords

Vitamin D intake, calcium intake, cohort study, breast cancer risk, diet

Introduction

Both epidemiological and experimental data suggest an inverse association between vitamin D and breast cancer (1-3). Besides its classical function on calcium homeostasis and bone metabolism, vitamin D has potential anticarcinogenic properties with regard to regulation of apoptosis, cell differentiation, cell growth and growth factor signaling (4-6).

Studies assessing the association of vitamin D intake and breast cancer risk have yielded inconsistent results. A meta-analysis from 2010 that pooled 11 studies assessing vitamin D intake from either diet and/or supplements and breast cancer risk resulted in a significant overall association with a RR of 0.91 (0.85 – 0.97) (7). However, there was no significant association when assessing vitamin D intake from diet only. Another meta-analysis from 2008 reported no statistically significant association between dietary vitamin D intake from food or supplements and breast cancer risk (8). A number of studies have assessed the relationship between breast cancer risk and serum vitamin D metabolites [25(OH)D or $1,25(OH)_2D$)], the biomarkers for vitamin D status in humans, which cover vitamin D from diet, supplements and from endogenous production after exposure to sunlight. Most case-control studies reported an inverse association between vitamin D status and breast cancer risk (9). However, there was no statistically significant inverse association in cohort studies (9), except for a recent study in the French E3N Cohort (10). In addition, the Second Expert Report by the World Cancer Research Fund (WCRF) classified the evidence as limited (no conclusion) for both pre- and postmenopausal breast cancer (11).

There is less scientific evidence with regard to the anticarcinogenic potential of calcium, though effects of calcium on cell proliferation and apoptosis have been reported (12, 13). However, due to the tight homeostasis of plasma calcium, it is unclear whether dietary calcium may affect breast cancer risk. Various studies assessed the association between dietary calcium intake and breast cancer risk with the majority reporting inverse associations (3). A meta-analysis pooling data from 6 cohort and 9 case-control studies resulted in a

statistically significant inverse association between calcium intake and breast cancer risk. However, the results suggest an inverse association in pre- but not in postmenopausal women (7).

Vitamin D intake varies considerably across countries, which may also lead to different risk estimates (8). Furthermore, the amount of dietary calcium intake may affect the association between dietary vitamin D intake and breast cancer risk. We report here on the association between dietary vitamin D and calcium intake from foods and breast cancer risk in a heterogeneous population from different countries in Europe within the European Prospective Investigation into Cancer and Nutrition (EPIC). Due to its large sample size, EPIC provides the opportunity to investigate the association for both pre- and postmenopausal breast cancer risk. In addition to main effects, potential interaction effects between dietary vitamin D and calcium intake are addressed.

Material and methods

Study population

EPIC is a large prospective cohort study conducted since 1992 in 23 centers in 10 European countries [Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Great Britain (Cambridge, Oxford), Greece, Italy (Florence, Varese, Ragusa, Turin, Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), Sweden (Malmo, Umea), The Netherlands (Bilthoven, Utrecht)] with over 500,000 participants (14). Generally, the centers recruited the participants from the general population. However, French participants were members of a health insurance for school and university employees. Spain and Italy recruited participants among blood donors, members of several health insurance programs, employees of several enterprises, civil servants but also the general population. Participants were recruited from members of screening programs in Utrecht and Florence. In France, Norway, Utrecht, and Naples only women were included. Participants from Greece

were excluded due to missing validated information on vitamin D and calcium intake. Of the 342,686 female participants, we excluded 6,822 subjects with missing follow-up information, 15,019 subjects without dietary information, 837 subjects with in situ breast cancer, and 23 with not clearly malignant breast tumors (e.g. phyllodes tumors). Thus, the final cohort consisted of 319,985 participants.

Exposure assessment

Diet over the previous twelve months was assessed using dietary assessment instruments that were specifically developed for each participating country (14). The questions were structured by common food groups except for the questionnaires used in Italy and Spain, where questions were structured by country-specific meals.

All participants were asked to report their average consumption of each food item over the previous twelve months by structured categories ranging from never or less than once per month to six or more times per day. All dietary measurement instruments have been validated previously in a series of studies within the various source populations participating in EPIC (15).

To collect information on education, medical history (surgeries and previous illnesses), tobacco and alcohol consumption, and physical activity and other lifestyle factors, a further questionnaire was used. Height and weight were measured at baseline, except for most participants recruited at the Oxford study center, and in France as well as all participants recruited in Norway. Self-reported data were available for the latter centres (14).

Menopausal status at baseline was defined as described previously using an algorithm that accounts for information on menstrual status/history, type of menopause, use of oral contraceptives and menopausal hormones (16).

Outcome assessment

In most countries (Denmark, Italy, The Netherlands, Norway, Spain, Sweden, and the UK) incident cancers were identified through linkage with population registries. Cancer cases were further identified by active follow-up, through a health insurance company (France) or direct contacts with study subjects, their doctors or their next of kin (France, Germany, and Greece). Mortality data were also obtained from either the cancer or mortality registries at the regional or national level. Participants from centers that relied on registry data that have been reported to IARC were censored between December 2002 and December 2005, depending on the study center. For Germany and Greece, the end of the follow up was considered to be the last known contact, the date of diagnosis, or the date of death, whichever came first. Cancer incidence was coded according to ICD-O-2.

Statistical analysis

Participants were categorized according to quintiles of dietary intake of vitamin D and calcium. Cox proportional hazards regression was used to examine the association of dietary intake of vitamin D or calcium and breast cancer risk. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, exit time was age when participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. Analyses were stratified by center to account for center effects such as follow-up procedures and questionnaire design, and by 1-year categories of age at recruitment to account for possible violations of the proportional hazard assumption.

Different models were run to fully disentangle the effects of dietary vitamin D and calcium on breast cancer risk: model 1, energy-adjusted only (kcal/day, quintiles); model 2, further adjustment for potential confounders and risk factors defined a-priori: total energy excluding energy from fat and alcohol (kcal/day, quintiles), fat (g/day, quintiles, monounsaturated,

polyunsaturated and saturated fat), alcohol consumption (g/day, quintiles), weight (kg, cont.), height (cm, cont.), smoking status (never, former, current, unknown), education level (none or primary school, technical/professional school, secondary school, longer education incl. university degree, unknown), menopausal status (premenopausal, perimenopausal, postmenopausal), total physical activity (inactive, moderately inactive, moderately active, active, missing), current use of oral contraceptives or hormones for menopause (yes, no, unknown), age at menarche (d12, 13-14, e15 years, missing); model 3, further adjustment on vitamin D (µg/day, quintiles) and calcium intake (mg/day, quintiles) in the calcium and vitamin D models, respectively. We adjusted for non-fat, non-alcohol energy and independently adjusted for alcohol and fat to account for both nutrients as potential confounders. In a sensitivity analysis we recalculated the models for all, pre- and postmenopausal women using the complete case analysis.

Multiplicative statistical interaction was evaluated with the likelihood-ratio-test by including cross-product terms of the potential interaction variables (continuous intake variables for vitamin D and calcium) in the respective models. Tests for trend were performed using the Wald statistic of the continuous intake variable.

In order to compare results across populations with different levels of sunlight exposure, the EPIC centres were divided into 7 latitude groups: below 42°N (Granada, Murcia, Ragusa, and Naples); 42°N - 44°N (Asturias, Navarra, San Sebastian, Florence, and South coast of France – centred in Marseille); 45°N - 46°N (Varese, Turin, and South of France – centred in Lyon); 47°N - 49°N (North-East and West of France – centred in Nantes and Paris, respectively – and Heidelberg); 50°N - 51°N (Potsdam, Utrecht, Bilthoven, Cambridge, and Oxford); 52°N - 56°N (Malmö, Aarhus, and Copenhagen); and above 57°N (Norway, and Umeå)

To correct for measurement error, FFQ dietary intake data were calibrated against 24-hour dietary recall data obtained from a random sample of the subcohort (N = 36,994). A fixed-effects linear model was used in which center and sex-specific 24-h recall data were regressed

on the FFQ intakes (17-19). The calibrated FFQ data were used to model dietary intake of vitamin D or calcium continuously. All tests were two-sided and considered to be statistically significant with a p-value of < 0.05. All analyses were performed in SAS software version 9.2 (Cary, NC, US).

Results

Mean follow-up time for the study population was 8.8 years. Mean time from baseline until breast cancer diagnosis was 5.1 years. During the follow-up, a total of 7,760 incident invasive (primary, malignant) breast cancer cases were identified, including 1,802 women who were premenopausal at recruitment and 4,259 cases in women who were postmenopausal at recruitment. Descriptive characteristics (at baseline) of the total cohort of 319,985 women are shown in Table 1. Women in the highest quintile of both vitamin D and calcium intake had a higher non-fat energy intake and a higher fat intake as compared to women in the lowest quintile. Furthermore, women in the lower quintile of vitamin D intake weighed less, used oral contraceptives less frequently, were younger at menarche, and were more often non-smokers.

As shown in Table 2, dietary vitamin D intake was highest in EPIC Sweden as compared to the other countries; calcium intake was highest in Denmark and the Netherlands.

Dietary vitamin D intake was not associated with overall breast cancer risk (p_{trend} = 0.92; Table 3), There was also no association when addressing pre- or postmenopausal women separately.

We found some indication for an inverse association between dietary calcium intake and breast cancer risk. The hazard ratio (HR) (95% confidence interval (CI)) for the highest as compared to the lowest quintile was 0.91 (0.83–1.01) (Table 3). The test for trend did not

reach statistical significance (p_{trend} = 0.06). Stratification by menopausal status indicated a possible association in postmenopausal women 0.90 (0.79–1.02), (p_{trend} = 0.05).

In the complete case analysis results were similar to those when using confounders with a category for missing data for both dietary vitamin D and calcium intake.

As dietary vitamin D may modify the association between calcium intake and breast cancer risk (and vice versa), we assessed potential interaction effects between both nutrients. However, statistical significant interaction (p-interaction = 0.44; 0.57 and 0.22 for all, premenopausal and postmenopausal women, respectively; data not shown) was not observed.

Moreover, additional adjustment by vitamin D (µg/day, quintiles) and calcium intakes (mg/day, quintiles) in the calcium and vitamin D models, respectively, did not result in changes of the risk estimates (data not shown).

To correct for potential measurement error, we repeated the analysis with the questionnaire data calibrated against 24-h recall data for the continuous intake variables. The overall associations were 1.00 (95% CI: 0.99-1.01; p = 0.92; uncalibrated) and 1.02 (95% CI: 0.99-1.06; p = 0.22; calibrated) per 1 µg/day increment of dietary vitamin D and 0.99 (95% CI: 0.99-1.00; p. = 0.06; uncalibrated) and 0.99 (95% CI: 0.97-1.00; p = 0.11; calibrated) per 100 mg/day increment of calcium intake.

In a country-specific analysis with the continuous calibrated intake values there was no statistically significant association between either vitamin D or calcium intake and overall breast cancer risk. Country-specific results by menopausal status also showed no significant associations except for an increased breast cancer risk associated with calcium intake in premenopausal women in the Netherlands (p = 0.01) (data not shown).

As a proxy for sun exposure and thus endogenous vitamin D production we divided the centres in 7 categories according to their latitude. Adjustment for latitude did not change the observed risk estimates for vitamin D and breast cancer risk. Moreover, we calculated

separate risk estimates for each latitude. There was no significant association between vitamin D and breast cancer risk in any of the latitude groups ($p_{heterogeneity} = 0.37$).

Discussion

The present study is so far the largest prospective study including data from nine European countries that assessed dietary vitamin D or calcium intake and breast cancer risk. Dietary vitamin D and calcium intake was not associated with breast cancer risk. There was also no significant interaction between both nutrients. Evidence for an association between dietary vitamin D intake and breast cancer risk has not been consistent in cohort studies, which reported a significant inverse association only in premenopausal women (20), in postmenopausal women with ER positive tumors (21) or no significant association at all (22-28). Four out of eight case-control studies, three of which included premenopausal women only, did not find an association (29-33), three reported significantly inverse associations (34-36), whereas one study reported a non-significantly increased risk with higher dietary vitamin D intake (37). A meta-analysis that pooled results from 11 studies assessing total vitamin D intake and breast cancer risk resulted in a significant overall inverse association with risk of 0.91 (0.85 – 0.97) (7). However, when differentiated by source of vitamin D, the significant inverse association was seen in vitamin D supplement users only but no association existed when analysing dietary vitamin D intake from foods. Also, a meta-analysis from 2008 reported no significant association between dietary vitamin D intake from food or supplements and breast cancer risk (8). However, the authors observed a significant inverse association when restricting the analysis to women taking more than 10µg/day vitamin D. Thus, the amount of dietary intake in the present population may be too low to detect a potential effect. Intake of dietary vitamin D in the present study was somehow comparable with dietary intake, but not total intake values reported in US studies (20, 21). In contrast,

dietary calcium intake in EPIC is somehow higher than reported dietary intake in the US (20, 21). Unfortunately, we did not have information on supplemental vitamin D intake nor on sun exposure as primary source of vitamin D. We, however, adjusted in the regression analysis for physical activity which may in part account for sun exposure, with a marginal effect on risk estimates. In a sensitivity analysis, we also adjusted for centers' latitude as another proxy for sun exposure, which also did not affect the risk estimates. Furthermore analyses were stratified by centres latitude which may in part account for differential effects of sun exposure by region. In contrast to Engel et al. (26), who observed a decreased postmenopausal breast cancer risk associated with vitamin D intake in regions with high ultraviolet radiation dose, we did not find any evidence for a differential effect of dietary vitamin D on pre- or postmenopausal breast cancer risk in regions with different sun exposure.

Studies accounting for total vitamin D status by measuring 25(OH)D in plasma or serum have yielded mostly significant inverse associations in case-control studies but, except for one study (10), no associations with risk in cohort studies (9).

We did not observe a statistically significant association between dietary calcium and breast cancer risk in pre- or postmenopausal women. However, we found some indication of an inverse association in postmenopausal women with borderline significance ($p_{trend} = 0.05$).

Most case-control studies reported an inverse association (37-46), although statistically significant only in a subset (40, 41, 45, 46) and no association was observed in three studies in premenopausal women only (30, 31, 34). Cohort studies reported a reduced risk of breast cancer associated with dietary calcium (20, 21, 24, 47, 48), including two studies in premenopausal women only (20, 24) and one in estrogen receptor-/progesterone receptor-negative tumors only (48), or no significant association (33, 49). The results of the largest trial so far, the Women's Health Initiative, did not demonstrate an inverse association between breast cancer risk and calcium plus vitamin D supplementation (50). However, a recent reanalysis of the WHI data provided evidence for a protective effect of vitamin D and calcium

supplementation in women who were not taking further personal supplements, indicating that supplementation may only be effective in those women who were deficient (51).

Calcium might exert its potential anticarcinogenic properties via several mechanisms including effects on cell proliferation, apoptosis or cell differentiation (3, 12, 13). So far, differential anticarcinogenic mechanisms on pre- and postmenopausal breast cancer are not known. However, a meta-analysis pooling data from 15 studies reported a statistically significant inverse association in pre-/perimenopausal women but not postmenopausal women (7).

Further studies have concentrated on measurement of calcium in serum samples as a marker of a subject's calcium status (52-54). Results have been inconsistent, showing significant positive (53) or negative associations (52) in premenopausal women or no significant association at all (54). However, as the calcium metabolism and thus serum calcium levels are tightly regulated, blood levels of calcium may not be a good marker for calcium status or dietary calcium intake (55).

In line with previous studies, our results do not suggest an interaction between vitamin D and calcium intake (20, 33, 34), nor that the associations were confounded by each other. In contrast, another study reported a borderline significant interaction between both nutrients in postmenopausal women ($p = 0.05$) with a non-significant inverse association for calcium intake in the group with the highest tertile vitamin D intake (24).

Strengths of the study are its prospective design, the calibration of food frequency questionnaire data against 24-h-recall data to reduce measurement error, as well as the inclusion of participants from different European countries reflecting a wide range of intake.

However, several limitations have to be taken into account. We did not have information on the overall vitamin D status, including vitamin D from endogenous synthesis and vitamin D from supplements. Vitamin D supplementation varies across European countries. Especially

in the Northern countries, vitamin D from supplements, e.g. cod liver oil, is frequently used and thus one of the most important sources of vitamin D (56). Since the contribution of diet to the overall vitamin D status of a person is limited (not more than 10-20% of vitamin D may originate from dietary sources), studies with information on the entire vitamin D status may come to another conclusion. Moreover, we assessed nutrient intake at only one point in life time. It is currently unknown at what point in time vitamin D or calcium intake may affect breast cancer risk. However, a recent study measuring ultraviolet sunlight exposure as a proxy for vitamin D production suggest that exposure in both adolescence and adulthood may reduce breast cancer risk (57)

In summary, the present study does not support an association of dietary vitamin D or calcium intake with breast cancer risk. Further research assessing vitamin D and breast cancer risk should focus on biomarker measurement to account for the overall vitamin D status as dietary intake may be too low to detect potential anticarcinogenic effects

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Table 1: Descriptive characteristics of the EPIC cohort according to the lowest and highest vitamin D and calcium intake

	Total cohort	Dietary vitamin D intake[3]		Dietary calcium intake[3]	
		Lowest quintile	Highest quintile	Lowest quintile	Highest quintile
Age (years), mean (SD)	50.2 (9.7)	48.9 (10.7)	50.3 (9.4)	49.1 (8.9)	50.9 (9.9)
Height (cm), mean (SD)	162.6 (6.6)	161.0 (6.6)	164.7 (6.3)	162.5 (6.7)	163.1 (6.5)
Weight (kg), mean (SD)	65.5 (11.6)	63.1 (11.2)	67.7 (11.8)	65.8 (11.7)	65.9 (11.8)
Ethanol intake (g/d), mean (SD)	8.3 (11.8)	7.7 (11.8)	6.7 (10.1)	6.9 (11.1)	9.1 (12.3)
Non-fat energy intake (kcal/d), mean (SD)	1196 (342)	1079 (317)	1263 (330)	919 (233)	1496 (340)
FAMS (g/d), mean (SD)	27.4 (11.1)	23.8 (10.1)	28.7 (10.5)	20.8 (8.1)	34.3 (12.6)
FAPU (g/d), mean (SD)	13.5 (5.9)	11.8 (5.9)	15.6 (5.9)	10.9 (4.8)	16.0 (6.6)
FASAT (g/d), mean (SD)	29.7 (11.8)	23.9 (9.7)	33.0 (12.4)	20.9 (7.5)	39.8 (13.1)
Education[1]					
Primary school completed (%)	24.0	25.3	25.4	29.0	20.6
University degree (%)	23.0	27.4	17.6	18.7	25.1
Missing (%)	4.5	5.5	3.0	3.3	4.7
Smoking status					
Never (%)	54.8	62.3	44.9	49.2	56.2
Former (%)	23.4	20.4	26.5	23.2	24.2
Current (%)	19.6	15.4	26.0	25.1	17.5
Missing (%)	2.2	1.9	2.5	2.5	2.1
Age at menarche					
d12 years (%)	35.2	39.4	29.4	33.5	35.7
13-14 years (%)	46.1	46.2	47.6	46.6	45.8
e15 years (%)	15.2	13.3	18.0	15.7	15.7
Missing (%)	3.5	1.2	5.0	4.2	2.9
Current use of oral contraceptives/hormones for menopause					
Yes	22.1	20.0	23.7	22.9	21.8
No	71.4	76.1	68.2	69.8	72.7
Missing (%)	6.5	3.9	8.1	7.4	5.6
Physical activity[2]					
Inactive (%)	12.2	14.5	7.2	10.7	12.0
Moderately inactive (%)	29.6	36.4	17.4	22.0	33.3

Moderately active (%)	34.6	39.4	26.9	28.4	38.7
Active (%)	7.6	7.1	7.2	5.1	10.9
Missing (%)	16.0	2.6	41.2[2]	33.8[2]	5.1

[1] not all degrees listed, [2] physical activity data from Norway and 47% from Sweden are missing, in Norway calcium intake was low, and in Sweden and Norway vitamin D intake high, thus missing categories differ strongly between the quintiles; [3] Dietary intake from FFQ data, FAMS = monounsaturated fatty acids, FAPU = polyunsaturated fatty acids, FASAT = saturated fatty acids

Table 2: Dietary vitamin D and calcium intake in the respective countries of the EPIC cohort

	N, total cohort	Follow-Up time in person years	N, breast cancer cases	Vitamin D intake (µg/day) Mean [1]	Calcium intake (mg/day) Mean [1]
Denmark	28,694	215,799	822	4.67	1010
France	67,696	739,238	2844	2.68	907
Germany	27,864	227,045	455	3.63	959
Italy	30,434	256,918	673	2.08	818
Norway	35,226	210,297	470	4.15	808
Spain	24,809	241,082	316	5.00	981
Sweden	26,287	270,596	679	7.15	938
The Netherlands	26,432	228,577	564	4.31	1046
United Kingdom	52,543	441,127	937	3.74	968

[1] dietary intake from foods; data derived from 24-h diet recalls obtained in a subcohort (N = 36,994)

Table 3: Dietary vitamin D and calcium intake and risk of pre- and postmenopausal breast cancer

Vitamin D (µg/day)			All women						Premenopausal women			Postmenopausal women		
			Model 1[1]			Model 2[2]			Model 2[2]			Model 2[2]		
			HR	95 % CI		HR	95 % CI		HR	95 % CI		HR	95 % CI	
Quintiles (range)	Median intake	Cases (N)												
Q1 (<1.85)	1.35	1563	1.00			1.00			1.00			1.00		
Q2 (1.85 - <2.69)	2.27	1640	0.95	0.88	1.02	0.94	0.87	1.01	0.98	0.85	1.13	0.90	0.82	0.99
Q3 (2.69 - <3.68)	3.15	1673	1.02	0.95	1.10	1.01	0.94	1.09	1.14	0.99	1.32	0.97	0.87	1.07
Q4 (3.68 - <5.46)	4.39	1531	1.00	0.93	1.09	0.99	0.91	1.08	1.04	0.88	1.23	0.99	0.89	1.11
Q5 (e 5.46)	7.35	1353	1.03	0.94	1.13	1.04	0.94	1.14	1.07	0.87	1.32	1.02	0.90	1.16
p for trend[3]			0.92			0.92			0.78			0.21		
Calcium (mg/day)														
Quintiles (range)														
Q1 (<635)	516	1281	1.00			1.00			1.00			1.00		
Q2 (635 - <815)	730	1543	1.02	0.94	1.10	1.00	0.92	1.08	0.97	0.82	1.13	1.01	0.91	1.12
Q3 (815 - <992)	900	1575	0.96	0.88	1.04	0.93	0.86	1.01	0.92	0.77	1.09	0.94	0.84	1.05
Q4 (992 - <1,231)	1,097	1640	0.94	0.87	1.03	0.92	0.84	1.00	0.85	0.70	1.02	0.95	0.85	1.07
Q5 (e 1,231)	1,440	1721	0.93	0.85	1.02	0.91	0.83	1.01	0.98	0.80	1.19	0.90	0.79	1.02
p for trend[3]			0.05			0.06			0.85			0.05		

[1] Cox proportional hazard model stratified by age and center adjusted for energy intake (kcal/day, quintiles)
[2] Cox proportional hazard model stratified by age and center, adjusted for no-fat, no-alcohol energy (kcal/day, quintiles), fat (g/day, quintiles, monounsaturated, polyunsaturated, and saturated fat), alcohol consumption (g/day, quintiles), weight (kg, cont.), height (cm, cont.), smoking status (never, former, current, unknown), education level (none or primary school, technical/professional school, secondary school, longer education incl. university degree, unknown), menopausal status (premenopausal, postmenopausal, perimenopausal), current use of contraceptives or hormones (yes, no, unknown), physical activity (occupational, recreational and household activity; inactive, moderately inactive, moderately active, active, missing), age at menarche (d12, 13-14, e15, missing)
[3] Wald statistic of the continuous variable.
HR=hazard ratio, CI=confidence interval, 1 µg vitamin D = 40 IU vitamin D